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Identification and analytical properties of new synthetic cannabimimetics bearing 2,2,3,3-tetramethylcyclopropanecarbonyl moiety

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ABSTRACT

By means of gas chromatography with mass spectrometry detector (GC–MS), liquid chromatography–mass spectrometry (LC–MS) and nuclear magnetic resonance spectroscopy (NMR), structure of a series from a novel class of synthetic cannabimimetics bearing 2,2,3,3-tetramethylcyclopropanecarbonyl moiety was established. It was found that this fragment could undergo thermal ring-opening into isomeric structures. The title compounds under action of hydrochloric acid can transform into new compounds which structure is discussed in the paper. The compounds identified could be referred to a new class of 'designer drugs' and are in illegal turnover in Russia and Belarus since the summer of 2011. Analytical data obtained in the paper will make possible reliable identification of such new 'designer drugs' during forensic examination.

1. Introduction

Cannabimimetics have become very popular for non-medical usage as psychoactive drugs since 2008 [1,2]. This was especially favored by active development of a network of websites and online trading platforms, which distribute so-called 'legal' plant mixtures and chemicals. Numerous occurrences of these 'designer drugs' were detected in many countries including Russia and Belarus. These compounds are basically indole derivatives such as 3-naphthoylindoles, 3-phenylacetylindoles, 3-benzoylindoles and 3-adamantoylindoles [3–19].

Constant including of such indole derivatives into national black lists of illegal drugs has lead to occurrence of new class of synthetic cannabimimetics, modifications of 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole (**1**) (Table 1), first in Russia and later in Belarus.

In June 2011, FDCS officers in Ekaterinburg have made a test purchase of a sample of smoking mixture in a kiosk selling 'legal' smoking and aromatizing mixes. The sample was found to contain a cannabimimetic 'JWH-210' which is forbidden in Russia. Further search has revealed packets with plant mixes and a packet with a powder which was later identified as (1-pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (**2**) (our symbolic notation 'TMCP-018'). According to [20,21] the compound acts as a selective full agonist of the cannabinoid receptors CB_2 and CB_1. Later smoking mixes containing 'TMCP-018' became extremely widely spread in Russia with a maximum in February 2012: only in Ekaterinburg there were 2–5 seizures daily.

Bioactivity and methods of synthesis of derivatives of 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole compounds are described in the patents and the other literature [20–23]. According to these references 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole derivatives possess strongly pronounced physiological activity similar to Δ^9-tetrahydrocannabinol. NMR spectra of some compounds are also described in the literature, but there is no other spectral analytical data, which could enable reliable identification of these new classes of drugs.

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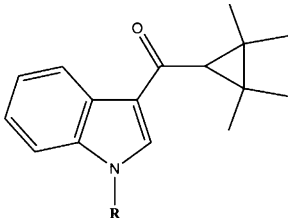
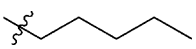
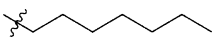
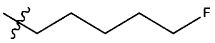
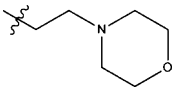
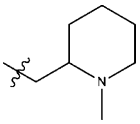
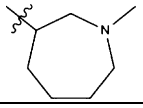
Table 1
Chemical structure of substances **1**–**7**.



No.	Short name	R	Chemical names
1	TMCP-H	H	(1*H*-Indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
2	TMCP-018		(1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
3	TMCP-020		(1-Heptyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
4	TMCP-2201		[1-(5-Fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
5	TMCP-200		[1-(2-Morpholin-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
6	TMCP-1220		[1-(1-Methylpiperidin-2-ylmethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
7	TMCP-1220-azepane		[1-(1-Methylazepan-3-yl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone

We have identified that since the summer 2011 most popular compounds, from the class, were: 'TMCP-018' (**2**), parent 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole (**1**) and the other derivatives thereof (**3**–**7**), as well as {*N*-[3-(2-methoxyethyl)-4,5-dimethylthiazol-2(3*H*)-ylidene]-2,2,3,3-tetramethylcyclopropanecarboxamide} (**8**) ('A-836,339'), a thiazolidene analog of the compounds under discussion (Fig. 1). Also there were cases of occurrence the products of thermal and acidic transformation of compounds **1**–**7**, in illegal turnover.

For the other identified compounds, the we give symbolic notations following structural analogy with known synthetic cannabimimetics of 'JWH' and 'AM' series: 'TMCP-020' – (1-heptyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (**3**), 'TMCP-2201' – [1-(5-fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (**4**), 'TMCP-200' – [1-(2-morpholyn-4-ylethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone (**5**), 'TMCP-1220' – [1-(1-methylpyperidin-2-ylmethyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (**6**), 'TMCP-1220-azepane' – [1-(1-methylazepan-3-yl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone (**7**).

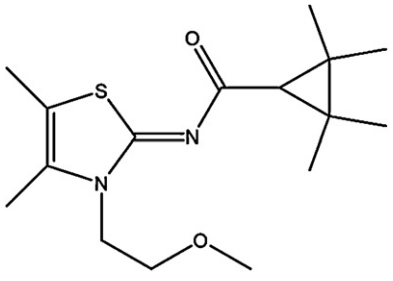


Fig. 1. Chemical structure of 'A-836,339' (substance **8**).

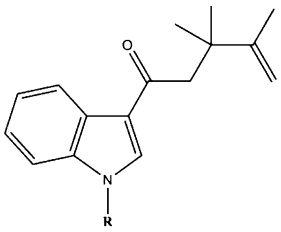
These compounds were detected in numerous real evidences both in pure powders and in smoke mixtures. These compounds are often found in plant mixes in a combination with the other known cannabimimetics of 'JWH' and 'AM' series.

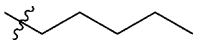
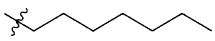
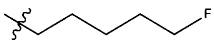
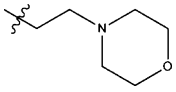
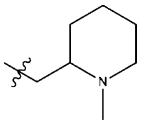
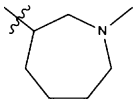
We have found that strained cyclopropyl ring in compounds **1**–**7** tends to undergo ring-opening into isomers **9**–**15**, at thermal treatment (>150 °C) (Table 2). We suggested that similar process takes place during any part of preparation and use of illegal herbal products, adulterated with synthetic cannabimimetics **1**–**7** where overheating is possible: synthesis, application of compounds to a plant matrix, drying from solvents and smoking. Actually, analysis of some samples of criminal smoke mixtures has revealed not only original cannabimimetics **1**–**7** but also thermally stable isomers **9**–**15** thereof – as major components. Moreover, the samples from some seized smoking tools were found to contain isomers **9**–**15** only. This brought us to a suggestion that the latter possess strong psychoactivity.

In some criminal samples, we have found a compound with presumable structure of (*E*)-1-pentyl-3-[4,4,5,5-tetramethyldihydrofuran-2(3*H*)-ylidene]-3*H*-indol-1-ium chloride (**16**) (Fig. 2, symbolic notation 'TMCP-018 acidic'), which – as we have shown later in the experiment – could be prepared under action of hydrochloric acid onto 'TMCP-018'. The acidic recyclization of α-carbonylcyclopropyl found is similar to the process described in the literature [24].

In current paper, we give analytical properties of above-mentioned compounds obtained by means of GC–MS, LC–MS and NMR spectroscopy which would help official experts to determine

Table 2
Chemical structure of substances **9**–**15**.



No.	Short name	R	Chemical name
9	TMCP-H (thermal isomer)	H	1-(1*H*-Indol-3-yl)-3,3,4-trimethylpent-4-en-1-one
10	TMCP-018 (thermal isomer)		3,3,4-Trimethyl-1-(1-pentyl-1*H*-indol-3-yl)pent-4-en-1-one
11	TMCP-020 (thermal isomer)		1-(1-Heptyl-1*H*-indol-3-yl)-3,3,4-trimethylpent-4-en-1-one
12	TMCP-2201 (thermal isomer)		1-[1-(5-Fluoropentyl)-1*H*-indol-3-yl]-3,3,4-trimethylpent-4-en-1-one
13	TMCP-200 (thermal isomer)		3,3,4-Trimethyl-1-[1-(2-morpholin-4-ylethyl)-1*H*-indol-3-yl]-pent-4-en-1-one
14	TMCP-1220 (thermal isomer)		3,3,4-Trimethyl-1-[1-(1-methylpiperidin-2-ylmethyl)-1*H*-indol-3-yl]pent-4-en-1-one
15	TMCP-1220-azepane (thermal isomer)		3,3,4-Trimethyl-1-[1-(1-methylazepan-3-yl)-1*H*-indol-3-yl]pent-4-en-1-one

composition of psychoactive compounds and conversion products thereof.

2. Materials and methods

2.1. Materials

Individual substances were sampled from evidences brought for examination to the expert laboratories of Ekaterinburg (Russian Federation) and Minsk (Belarus). Preliminary control was performed by GC–MS and TLC (eluent, hexan – acetone, 5:1) on silica gel plates 'Sorbfil TLC-P-UV' (Russian Federation).

Criminal samples in form of white microcrystal powders were put into NMR-investigations as they were (without additional purification) when preliminary analyses by means of GC–MS, LC–MS and TLC (eluent, hexane – acetone, 5:1) proved their uniformity.

Compounds **9**–**15** were prepared from compounds **1**–**7** correspondingly by heating the latter at 180 °C during 30 min in conventional thermal cabinet in ambient atmosphere.

For the purpose of determination of the structure, compound **16** was prepared from individual 'TMCP-018' (**2**) by refluxing the former in two-phase mixture of chloroform and hydrochloric acid in a water bath until complete evaporation of chloroform. Compound **16** completely dissolves in water phase and for its isolation,

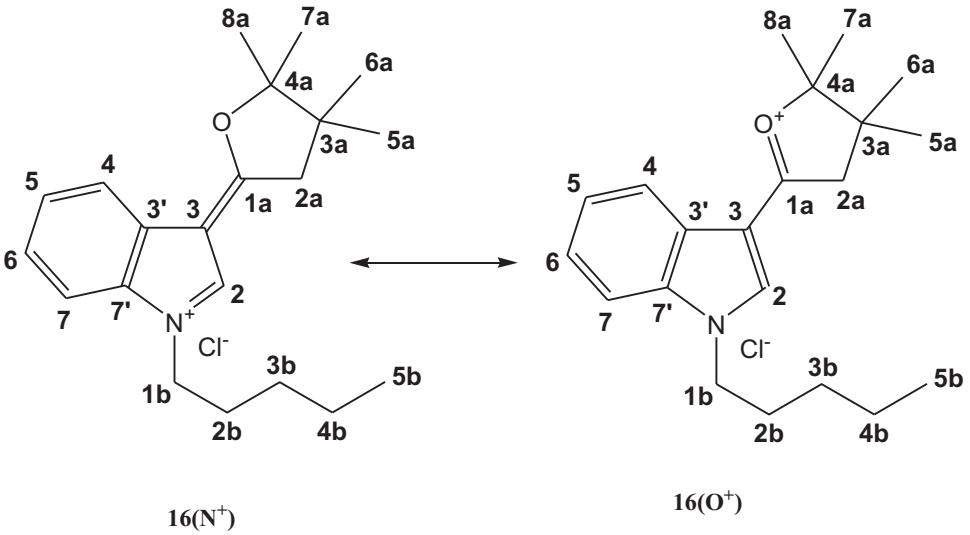


Fig. 2. Presumable resonance structures of 'TMCP-018 acidic' (compound **16**).

the solution was diluted with a plenty of water and extracted with chloroform. Compound **16** could be prepared by analogous procedure from compound **10**. Together with the sample thus obtained, we have investigated individual sample of compound **16** of criminal origin.

2.2. Solvents

Methanol was purchased from Merck KGaA (Germany), hexane – from Cryochrom (Russian Federation), acetone – from Ekos (Russian Federation), water for GC, HPLC and Spectrophotometry – from Honeywell Burdick and Jackson (USA), acetonitrile HPLC-gradient grade – from Panreac (Spain), formic acid puriss. – from Sigma–Aldrich (Germany). All solvents had a grade not less than 'pure for analysis' (analytical grade). For recording NMR spectra, $CDCl_3$ with isotopic purity 99.8%, with admixture of 0.03% TMS was used (Sigma–Aldrich GmbH, Seelze, Germany). For determination of chromatography retention indices, a set of individual *n*-alkanes (Fluka, Sigma–Aldrich, Steinheim, Germany) was used as a standard.

2.3. Instruments and methods

Liquid chromatography–mass spectrometry (LC–MS) measurements were performed with a 6540 accurate mass Q-TOF LC–MS instrument (Agilent Technologies). Chromatographic separation was performed using a Agilent 1290 Infinity ultra-high performance liquid chromatography system at 50 °C with an Zorbax Extend-C18 RRHT, 2.1 mm × 50 mm, 1.8 μm, column (Agilent 727700-902). For gradient elution, the mobile phases 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) were used with the time program: 0 min 10% B, linear to 15% B at 1 min, linear to 100% B at 19 min, constant 100% B to 20 min, back to 10% B and equilibration for 2 min. The flow rate was 0.5 ml/min. The spectra were measured by flow injection of 5 ng of each substance (1 μl of 5 μg/ml solution in methanol).

The QTOF-MS instrument was operated with an electrospray ion source ESI in positive ionization mode. Nitrogen was used as the drying gas at a temperature of 350 °C and flow 10 l/min and nebulizing gas with a pressure of 40 psi. Capillary voltage was set at 3500 V and skimmer voltage at 65 V. Quadrupole was used as an ion guide in MS mode. A fragmentor voltage was set at 100 V. The remaining instrument conditions were: mass range 100–1700 *m/z*, scan rate 2 Hz (EDR). Spectra were internally mass corrected in real time using an automatically introduced reference mass solution containing two compounds: purine ($[M+H]^+$ = 121.050873) and HP-921 – hexakis (1*H*,1*H*,3*H*-tetrafluoropropoxy)phosphazine ($[M+H]^+$ = 922.009798).

GC–MS analysis was performed using a 7820A gas chromatograph (GC) with a 5975 mass selective detector (MSD) purchased from Agilent Technologies. The MSD was operated in the electron ionization (EI) mode with an ionization potential of 70 eV, a scan range of 20–550 amu. The ion source temperature was maintained at 230 °C.

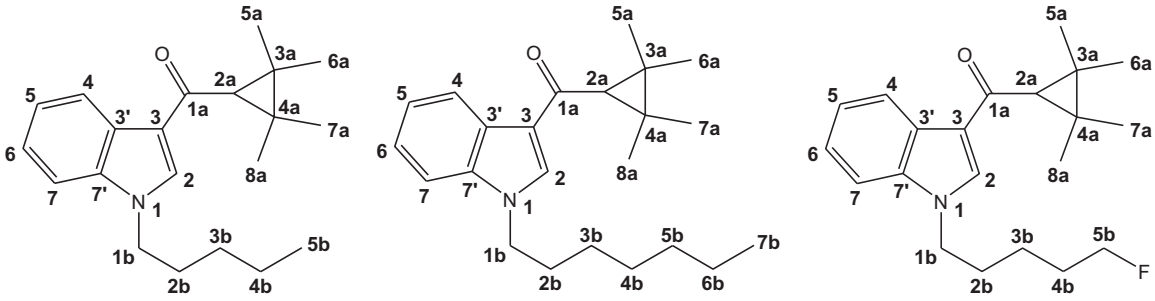
Chromatographic separation was carried out using a capillary column HP-5MS (30 m × 0.25 mm × 0.25 μm, Agilent 19091S-433). The GC was operated in split mode (50:1) with a helium flow rate at 1.0 ml/min (constant flow). The GC injector temperature was maintained at 280 °C and the transfer line at 280 °C.

The oven temperature was programmed as follows: initial temperature, 100 °C; initial hold, 2.0 min; program rate, 20 °C/min; final temperature, 290 °C; final hold, 20 min. Total run time was 31.5 min.

^1H and ^{13}C NMR spectra were recorded on Bruker Avance II spectrometer in $CDCl_3$ (400 and 100 MHz, respectively) using TMS (for ^1H and ^{13}C) or $CFCl_3$ (for ^{19}F) as an internal standard. ^{13}C NMR spectra were recorded in *J*-mode (APT). ^{19}F NMR spectra were recorded with decoupling from protons. Final assignment of the

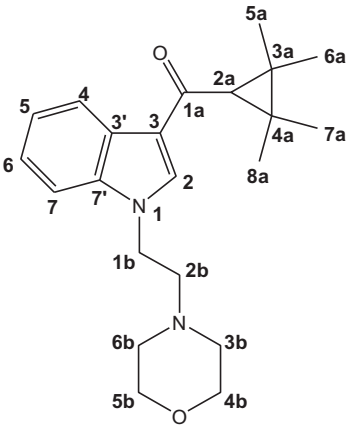
Table 3
NMR spectral data for compounds **2**, **3** and **4**.

C atom no.



	TMCP-018 (**2**)		TMCP-020 (**3**)		TMCP-2201 (**4**)		
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^{19}F
2	7.69 (s., 1H)	133.6	7.68 (s., 1H)	133.4	7.67 (s., 1H)	133.5	
3		119.8		119.7		119.9	
3′		126.5		126.4		126.5	
4	8.42–8.46 (m., 1H)	122.8	8.40–8.46 (m., 1H)	122.7	8.40–8.44 (m., 1H)	122.9	
5	7.27–7.32 (m., 1H) overlapped	122.2	7.24–7.32 (m., 1H) overlapped	122.0	7.23–7.30 (m., 1H) overlapped	122.3	
6	7.27–7.32 (m., 1H) overlapped	123.0	7.24–7.32 (m., 1H) overlapped	122.9	7.23–7.30 (m., 1H) overlapped	123.1	
7	7.34–7.39 (m., 1H)	109.8	7.32–7.37 (m., 1H)	109.6	7.32–7.36 (m., 1H)	109.7	
7′		136.8		136.6		136.7	
1a		194.7		194.6		194.8	
2a	1.98 (s., 1H)	41.8	1.97 (s., 1H)	41.7	1.95 (s., 1H) overlapped	41.8	
3a, 4a		31.6		31.7		31.8	
5a, 6a	1.39 (s., 6H)	24.2	1.38 (s., 6H)	24.1	1.36 (s., 6H)	24.2	
7a, 8a	1.34 (s., 6H)	17.2	1.33 (s., 6H)	17.1	1.31 (s., 6H)	17.2	
1b	4.16 (t., 2H, *J* = 7.2 Hz)	47.1	4.16 (t., 2H, *J* = 7.2 Hz)	47.0	4.18 (t., 2H, *J* = 7.2 Hz)	47.0	
2b	1.92 (quintet, 2H, *J* = 7.2 Hz)	29.8	1.91 (quintet, 2H, *J* = 7.2 Hz)	31.5	1.95 (quintet, 2H, *J* = 7.2 Hz) overlapped	29.8	
3b	1.34–1.44 (m., 2H) overlapped	29.2	1.25–1.41 (m., 2H) overlapped	30.0	1.45–1.55 (m., 2H)	23.0 (d., $^3J_{C\text{-}F}$ = 4.6 Hz)	
4b	1.34–1.44 (m., 2H) overlapped	22.4	1.25–1.41 (m., 2H) overlapped	28.8	1.66–1.82 (dm., 2H)	30.1 (d., $^2J_{C\text{-}F}$ = 19.9 Hz)	
5b	0.94 (t., 3H, *J* = 6.8 Hz)	14.0	1.25–1.41 (m., 2H) overlapped	26.9	4.38 and 4.50 (dt., 2H, ^2J = 47.6 Hz/^3J = 5.8 Hz)	83.8 (d., $^1J_{C\text{-}F}$ = 165.6 Hz)	−218.7
6b			1.25–1.41 (m., 2H) overlapped	22.5			
7b			0.90 (t., 3H, *J* = 6.8 Hz)	14.0			

Table 4
NMR spectral data for compound **5**.



C atom no.	TMCP-200 (**5**)	
	^{1}H	^{13}C
2	7.79 (s., 1H)	134.2
3		119.9
3′		126.4
4	8.42–8.45 (m., 1H)	122.9
5	7.25–7.33 (m., 1H) overlapped	122.3
6	7.25–7.33 (m., 1H) overlapped	123.1
7	7.34–7.39 (m., 1H)	109.5
7′		136.7
1a		194.8
2a	1.96 (s., 1H)	41.8
3a, 4a		31.7
5a, 6a	1.38 (s., 6H)	24.2
7a, 8a	1.33 (s., 6H)	17.2
1b	4.28 (t., 2H, J = 6.8 Hz)	44.4
2b	2.80 (t., 2H, J = 6.8 Hz)	57.9
3b, 6b	2.52 (t., 4H, J = 4.6 Hz)	53.9
4b, 5b	3.73 (t., 4H, J = 4.6 Hz)	67.1

spectra was made by two-dimensional experiments ^{1}H–^{13}C HMBC. Chemical shifts are presented in Tables 3–7.

3. Results and discussions

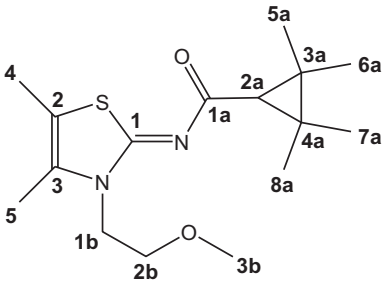
3.1. Gas chromatography and mass-spectrometry

GC analyses of compounds **1**–**7** gave pairs of peaks with close retention times and quite different intensity (Fig. 3). Electron ionization (EI) mass-spectrometry of the components within a pair showed that they have isobaric parent ions, and their fragmentation is characteristic in that is leads to a number of common ions. We have also noticed that decrease of the injector temperature decreases intensity of minor peak in GC (though not to its complete disappearance). These brought us to a suggestion that compounds **1**–**7** isomerize under action of the temperature in a course of analysis.

To prove this hypothesis, we have heated compound **2** at 180 °C, which lead to isomer **10**, which retention time and mass-spectrum were completely identical to the minor peak in GC–MS of compound **2**. Finally, the structure of compound **10** was proved by NMR-spectroscopy. Thus, major peaks in the pairs detected by GC correspond to original cyclopropyl structures **1**–**7** and the minor peaks (with somewhat higher retention times) belong to their thermal isomers **9**–**15**, which form at high temperatures.

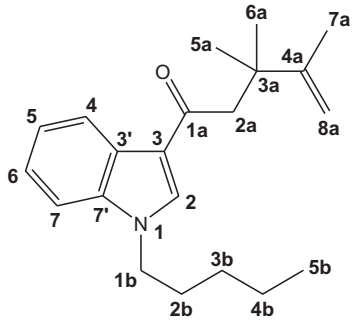
Similarity of the processes of ring-opening of cyclopropyl fragments in compounds **1**–**7** enabled us not only to register and

Table 5
NMR spectral data for compound **8**.



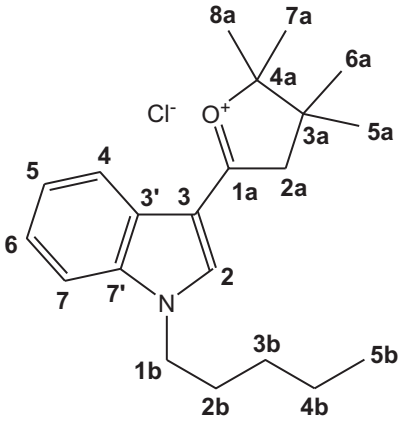
C atom no.	A-836,339 (**8**)	
	^{1}H	^{13}C
1		164.4
2		112.5
3		128.4
4	2.19 (s., 3H)	11.7
5	2.13 (s., 3H)	11.4
1a		181.4
2a	1.53 (s., 1H)	42.3
3a, 4a		30.1
5a, 6a	1.34 (s., 6H)	24.1
7a, 8a	1.21 (s., 6H)	17.0
1b	4.24 (t., 2H, J = 5.2 Hz)	46.3
2b	3.68 (t., 2H, J = 5.2 Hz)	70.2
3b	3.31 (s., 3H)	59.0

Table 6
NMR spectral data for compound **10**.



C atom no.	TMCP-018 thermal isomer (**10**)	
	^{1}H	^{13}C
2	7.71 (s., 1H)	134.6
3		118.1
3′		126.6
4	8.46–8.52 (m., 1H)	123.1
5	7.26–7.35 (m., 1H) overlapped	122.4
6	7.26–7.35 (m., 1H) overlapped	123.2
7	7.35–7.41 (m., 1H)	109.7
7′		136.7
1a		194.6
2a	2.92 (s., 2H)	49.6
3a		39.0
4a		152.6
5a, 6a	1.27 (s., 6H)	27.7
7a	1.87 (s., 3H)	20.0
8a	4.81 (d., 2H, J = 8.8 Hz)	109.1
1b	4.17 (t., 2H, J = 7.2 Hz)	47.1
2b	1.93 (quintet, 2H, J = 7.2 Hz) overlapped	29.6
3b	1.30–1.46 (m., 2H) overlapped	29.0
4b	1.30–1.46 (m., 2H) overlapped	22.3
5b	0.93 (t., 3H, J = 6.8 Hz)	13.9

Table 7
NMR spectral data for compound **16**.



C atom no.	TMCP-018 acidic (**16**)	
	^{1}H	^{13}C
2	10.27 (s., 1H)	156.0
3		108.9
3′		125.3
4	7.91–8.00 (m., 1H)	123.0
5	7.36–7.58 (m., 1H) overlapped	126.2
6	7.36–7.58 (m., 1H) overlapped	126.3
7	7.36–7.58 (m., 1H) overlapped	112.4
7′		139.1
1a		193.0
2a	4.29 (s., 2H)	49.6
3a		104.0
4a		42.6
5a, 6a	1.55 (s., 6H)	23.1
7a, 8a	1.24 (s., 6H)	23.0
1b	4.56 (t., 2H, J = 7.6 Hz)	49.2
2b	2.03 (quintet, 2H, J = 7.6 Hz)	29.4
3b	1.30–1.46 (m., 2H) overlapped	28.8
4b	1.30–1.46 (m., 2H) overlapped	22.3
5b	0.86 (t., 3H, J = 7.2 Hz)	13.9

interpret EI mass-spectra of original structures **1**–**7**, but also to detect MS of products of thermal transformation thereof without isolation of individual compounds **9**–**15** (with an exception of compound **10**).

EI mass-spectra, retention times (RT) and generalized log-linear indices (GI) of RT [25] are shown in Figs. 4 and 5.

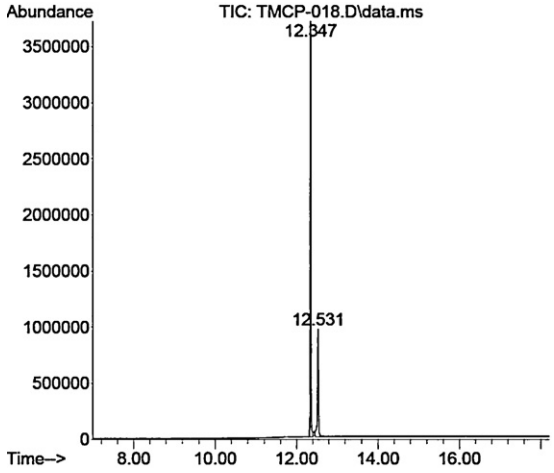


Fig. 3. Chromatogram of substance **2**.

Main trend in fragmentation of compound **1** and its *N*-alkyl substituted derivatives **2**–**4** as well as of compound **8**, is α-cleavage (typical to ketones) which leads to heterocyclic acyl ions. For compound **1**, the subsequent process is splitting CO from the acyl ion, while for compound **2**–**4** this process takes place after elimination of an olefin from *N*-acyl substituent. Such fragmentation leads to the ions with *m*/*z* 144 and 116 characteristic for 3-acylindole derivatives [3–19]. Along with this main route, we have detected significantly intense peaks with *m*/*z* $[M-15]^{+}$ which are, most probably, a consequence of elimination of methyl radical from the parent ion.

The processes described earlier are accompanied by a McLafferty rearrangement of compounds **9**–**12**, which leads to additional intense peak with *m*/*z* $[M-C_6H_{10}]^{+\bullet}$ (Fig. 6). The presence of these peaks, in mass-spectra of compounds **9**–**12**, is an evidence of acyclic structure formed in cleavage of the cyclopropyl ring.

EI mass spectra of compounds **5**–**7** and **13**–**15** bearing heterocyclic substituents in position 1 of indole ring are characterized basically in that the most intensive peaks there are those which form as a result of breaking the bond between the indole and heterocyclic parts of the molecule.

It is worthy to note that EI mass-spectra of compounds **5**, **6**, **13**, **14** resemble those for 'JWH-200' and 'AM-1220' [4,8,11] (which bear analogous heterocyclic substituents in position 1 of indole ring).

For example, MS spectra of compounds **6** and **14** are similar to spectrum of AM-1220 in that a peak with *m*/*z* 98, which corresponds to 1-methylpiperidin-2-ylmethyl fragment is the only intensive signal. In MS of compounds 7 and 15, similar to MS of azepane isomer of AM-1220 [11], parent ions give more intensive peaks – in comparison with compounds **6** and **14**. On the other hand, MS of compounds **7** and **15** differ from MS of azepane isomer of AM-1220 in lesser intensity of all peaks except for the peak corresponding to a fragment of heterocyclic ion (*m*/*z* 112). Peaks of ions which would correspond to cyclopropyl or alkenyl substituents at are not detected which could be explained with that these ions are less stable in comparison with naphthoyl from AM-1220 or its azepane isomer number. At the same time in MS spectra of compounds 7 and 15 – similar to MS of azepane isomer of AM-1220 – most peaks refer to azepane-indole fragment (*m*/*z* 184, 170, 144, 112, 98, 84, 70). This peculiarity is more pronounced in MS of compound **15**.

On contrary to 'AM-1220', compound **6** and its thermal isomer **14** in GC have retention times different from those for their azepane-isomers **7** and **15**, which makes additional sample preparation not necessary.

In an attempt to record GC–MS of (*E*)-1-pentyl-3-[4,4,5,5-tetramethyldihydrofuran-2(3*H*)-ylidene]-3*H*-indol-1-ium chloride (**16**), the greatest ion detected has *m*/*z* 311 which corresponds to the product of elimination of HCl from original structure **16** (which we named as **16-HCl**). We assume that elimination takes place in conditions of MS experiment.

3.2. NMR spectroscopy[1]

^{1}H NMR spectra of compounds **2**–**5** and **10** (Tables 3, 4 and 6) contain signals of five aromatic protons in the range 7.2–8.6 ppm. Their multiplicity and chemical shifts correspond to indol-3-yl fragment. Final confirmation of 3-acylindole structure was obtained from ^{13}C NMR spectra (Tables 3, 4 and 6): signals of five tertiary carbons in downfield (C-4, C-5, C-6, C-7 and C-2) along with signals of four quaternary carbons, corresponding to two

[1] NMR data were obtained in 'Laboratory of Complex Investigations and Expert Valuation of Organic Materials' of the Ural Federal University (Ekaterinburg, Russia).

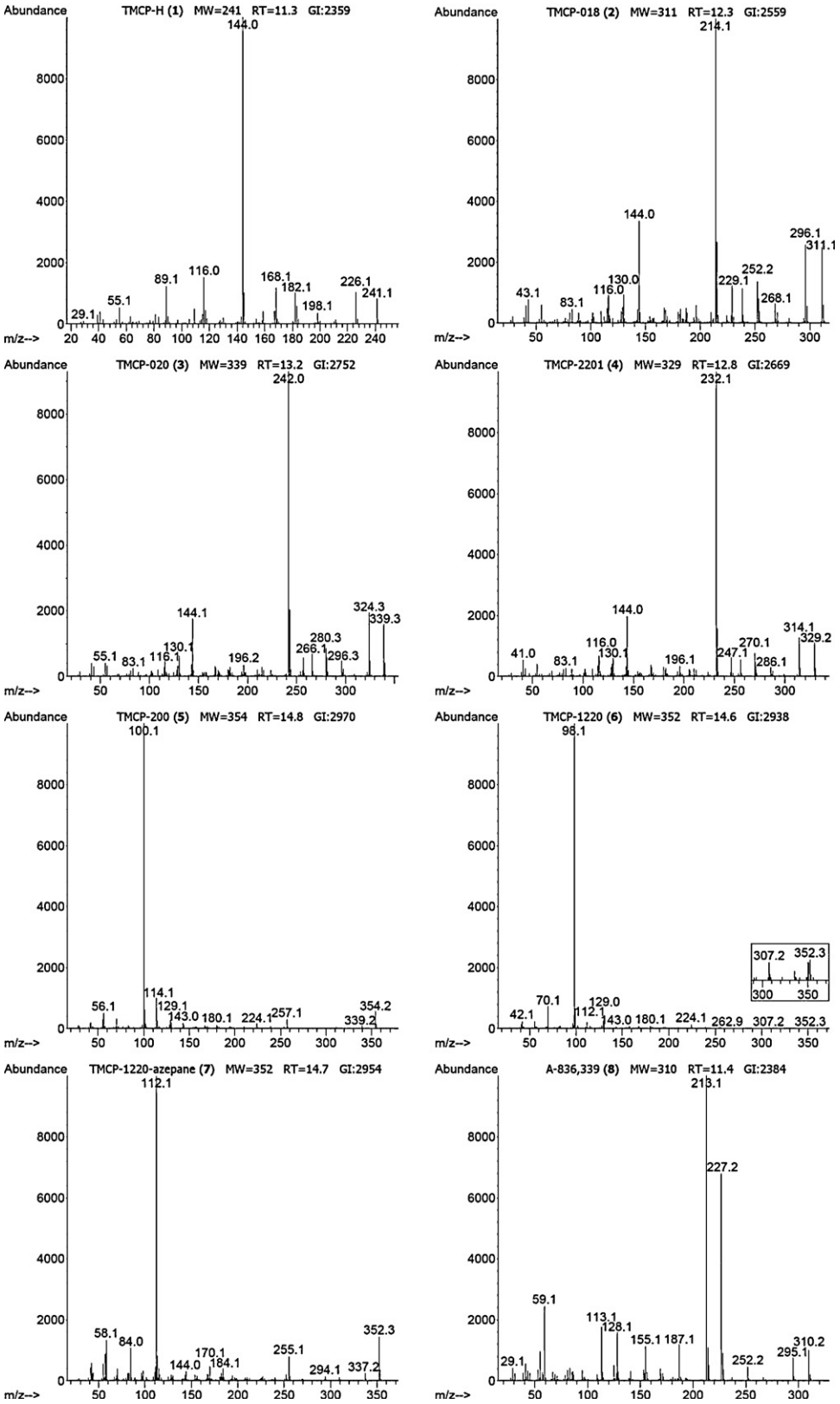


Fig. 4. MS, RT and GI of substances **1**–**8**.

junction carbons of benzene and pyrrole rings (C-3′ and C-7′), one carbon of indole (C-3) and one carbon from carbonyl group (C-1a).

Presence of 2,2,3,3-tetramethylcyclopropyl fragment was evidenced by one-proton singlet of methine proton in the range 1.95–1.98 ppm and two six-proton singlets of methine protons in the range 1.31–1.39 ppm in ^{1}H spectra of compounds **2**–**5**. Number of signals, their chemical shifts and degree of substitution for carbons, found in ^{13}C APT spectra completely correlate with suggested symmetrical 2,2,3,3-tetramethylcyclopropyl fragment.

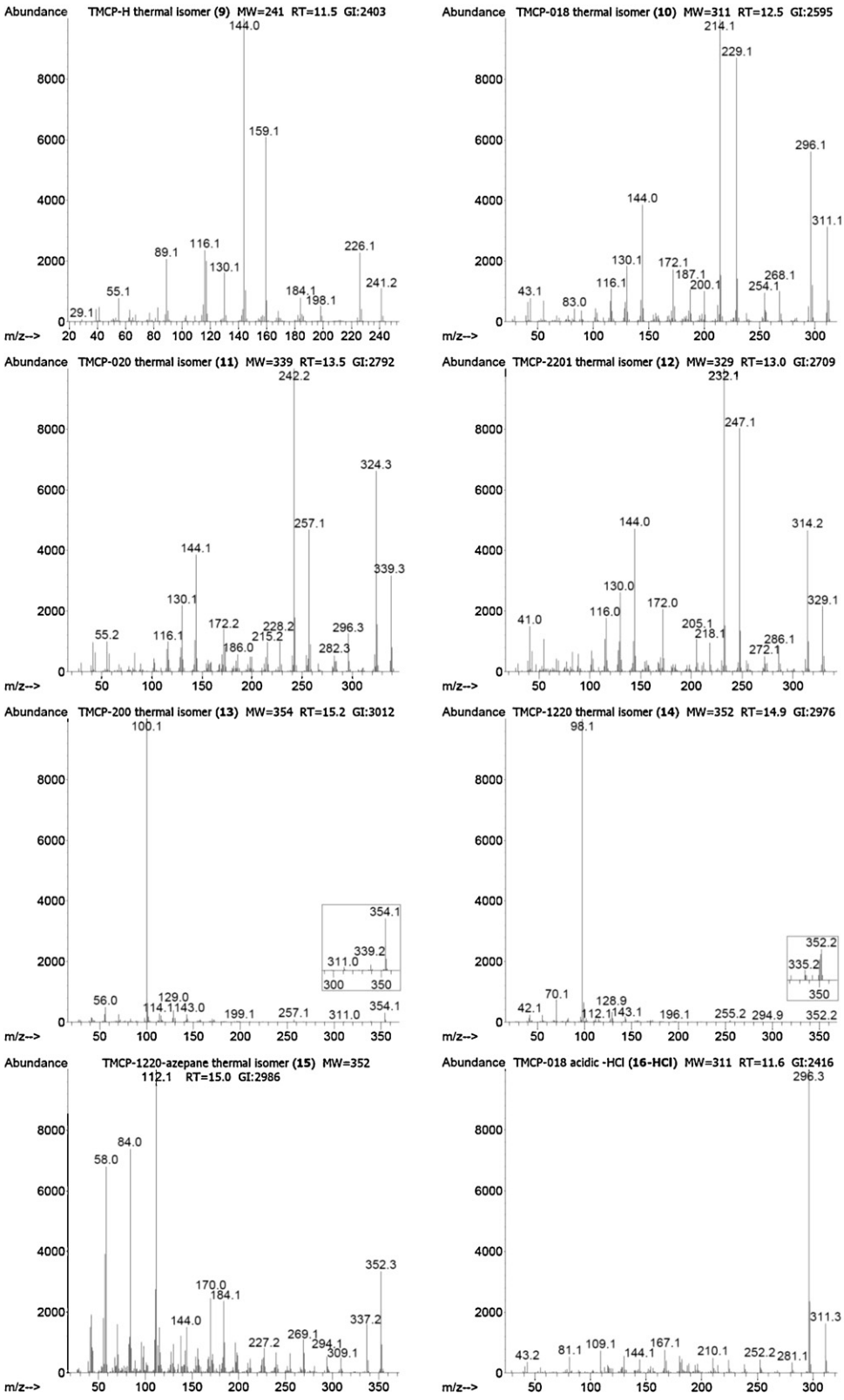


Fig. 5. MS, RT and GI of substances **9**–**15** and **16-HCl**.

Structure of substituents in position 1 of indole in compounds **2**–**5** and **10** was supported by signals found in ^{1}H, ^{13}C and ^{19}F NMR spectra (Tables 3, 4 and 6). Complete assignment of all signals was made basing on the analysis of 2D-experiments ^{1}H–^{13}C HMBC. Thus, for compound **2**, the following cross-peaks are most informative: H-2/C-3′, H-2/C-3, H-2/C-1a, H-2/C-1b, H-2/C-7′; H-2a/C-1a, H-2a/C-3, H-2a/C-3a,4a, H-2a/C-5a,6a and H-2a/C-7a,8a.

Cyclopropyl ring-opening in compound **2** and structure of acyclic product **10** were determined by NMR spectroscopy. Signals referring to indole and *N*-pentyl for the both compounds are identical (Table 6). Two-proton singlet at 2.92 ppm in ^{1}H NMR of

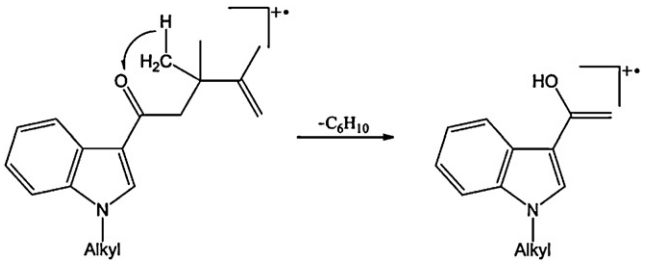


Fig. 6. The rearrangement scheme for substances **9**–**12**.

compound **10** assigned to hydrogens in α-position to carbonyl instead of one-proton singlet at 1.98 ppm in the spectrum of compound **2** assigned to corresponding hydrogen proves cleavage of cyclopropyl at this position. Cleavage of C–C bond and formation of C=C bond in γ-position to carbonyl are confirmed by two-proton doublet at 4.81 ppm together with three-proton singlet at 1.87 ppm in the spectrum of compound **10** instead of one of six-proton singlets in the spectrum of compound **2**. Double bond formation is also confirmed by downfield signals of a quaternary and secondary carbons at 152.6 and 109.1 ppm corresp., in ^{13}C spectrum of compound **10**. By analogy with compound **2**, analysis of 2D HMBC spectrum of compound **10** has revealed cross-peaks characteristic for *N*-alkyl-3-acylindole moiety: H-2/C-3′, H-2/C-3, H-2/C-1a and H-2/C-7′. It worthy to note new cross-peaks in 2D spectrum of compound **10** C-4a/H-2a, C-4a/H-5a,6a, C-4a/H-7a and C-4a/H-8a (Fig. 7) which serves an additional evidence of cyclopropyl ring-opening.

In ^{1}H NMR spectrum of compound **8** (Table 5), the signals of protons referring to 2,2,3,3-tetramethylcyclopropyl fragment are analogous to corresponding signals in compounds **2**–**5**. Two three-proton singlets of methyl groups and their chemical shifts confirm that they are attached to unsaturated bond in thiazolidene. Signals of methoxyethyl group linked to nitrogen of the heterocycle are found as relatively downfield singlet and two triplets. Number of signals and their chemical shifts, in ^{13}C NMR (APT) spectrum of compound **8** completely correlate with suggested structure.

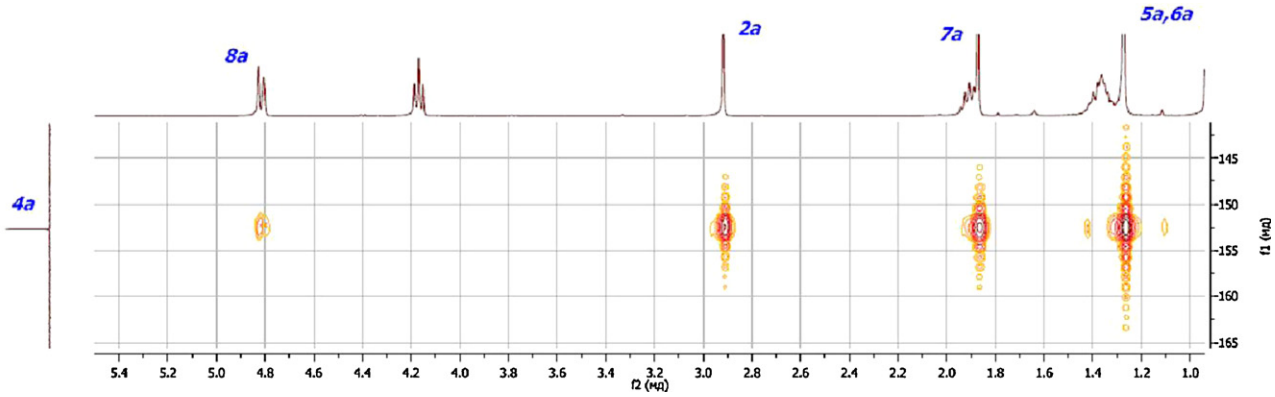


Fig. 7. Cross-peaks in NMR spectrum of compound **10**.

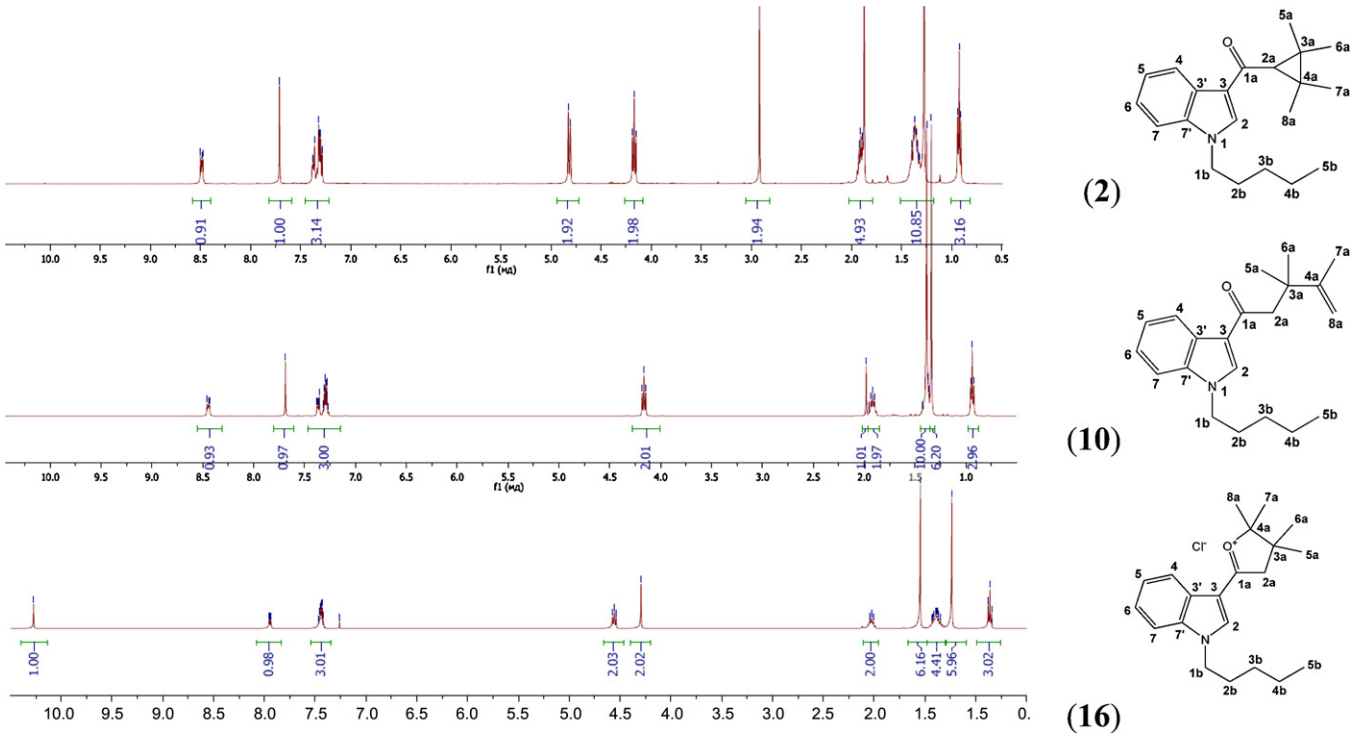


Fig. 8. Comparison of ^{1}H NMR spectra of compounds **2**, **10** and **16**.

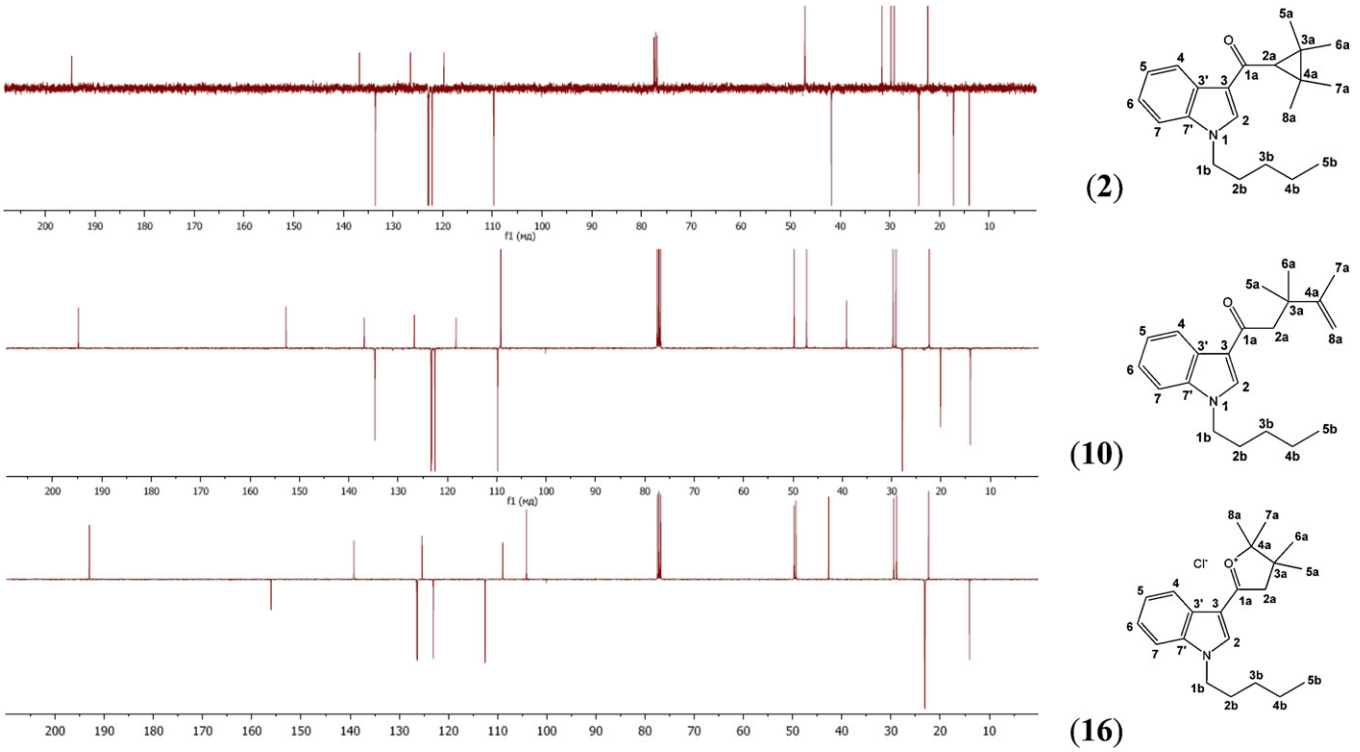


Fig. 9. Comparison of ^{13}C NMR spectra of compounds **2**, **10** and **16**.

In course of assignment of signals and determination of structure **16** (Table 7), certain inconsistency of spectral data was observed. Thus in MS of compounds **16**, **2** and **10** the same parent ion (*m*/*z* 311) was detected. On the other hand while most signals in ^{1}H NMR spectra of these compounds were similar in multiplicity and chemical shifts, one signal of a proton in spectra of compound **16** has shifted downfield significantly (Fig. 8). Namely, proton at C-2 of indole was detected at 7.69 ppm for compound **2**, at 7.71 – for 'thermal' compound **10** and at 10.27 ppm – for 'acidic' product **16**. Analogously, in ^{13}C NMR spectrum of compound **16** only two signals have shifted downfield in comparison with spectra of compounds **2** or **10**.

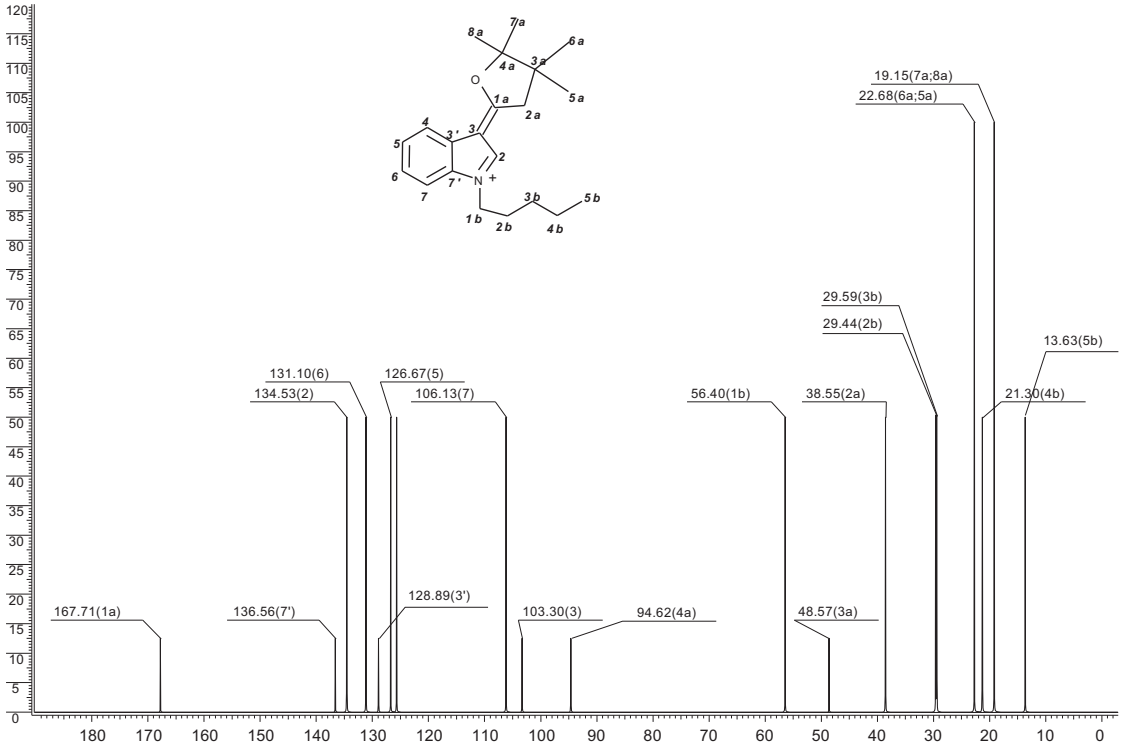


Fig. 10. ^{13}C NMR spectrum simulated for structure **16**(**N^{+}**).

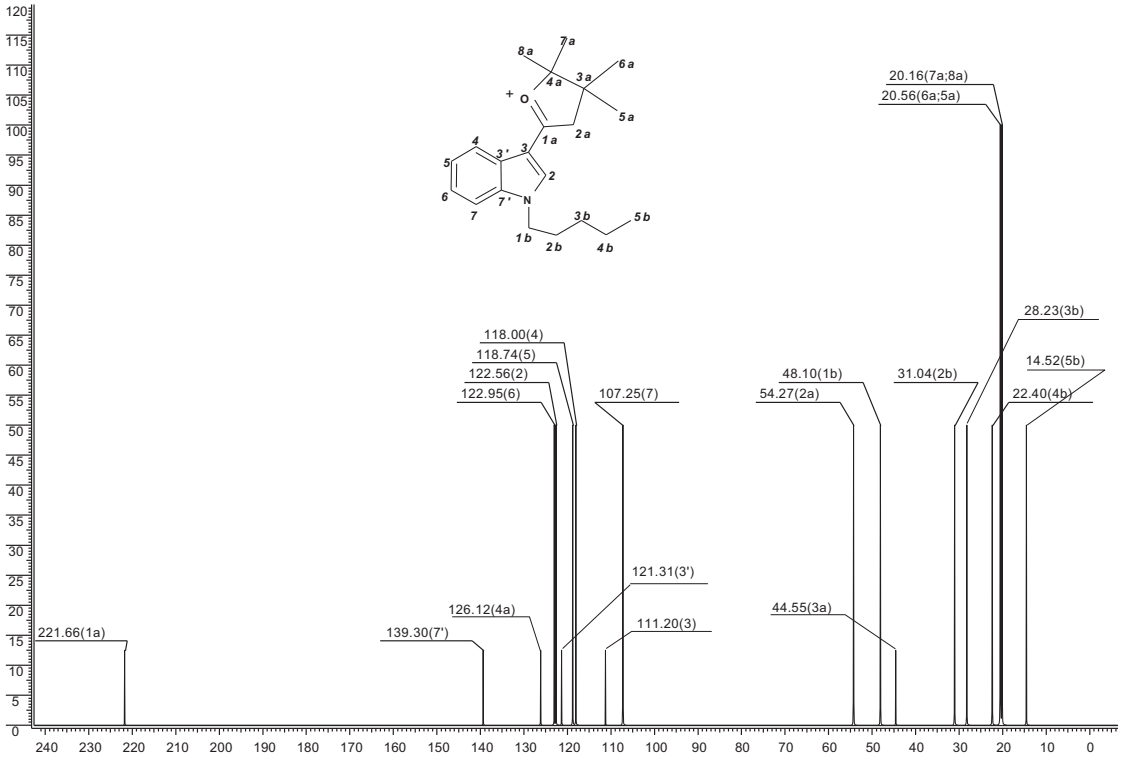


Fig. 11. ^{13}C NMR spectrum simulated for structure **16**(**O$^+$**).

In ^{13}C NMR spectra, signal of C-2 indole carbon for compound **2** (133.6 ppm) and for compound **10** (134.6 ppm) shifts to 156.0 ppm in spectrum of compound **16**, and signal of C-4a carbon for the same compound **16** (104.0 ppm) was observed in a field non-characteristic for sp^3-hybride carbons (Fig. 9).

Another peculiar feature of ^{13}C spectrum of compound **16** is too low chemical shifts of C-1a (193 ppm) and C-4a (104 ppm). These chemical shifts in ^{1}H and ^{13}C spectra of compound **16** are not characteristic for indole derivatives and differ substantially from the data for compounds **2** and **10** and from Refs. [20,26,27] data. We suggested that these could be rationalized by a mesomeric structure where positive charge is delocalized along a conjugation chain from indole N (resonance structure **16**(**N$^+$**)) to furan O (resonance structure **16**(**O$^+$**)) (Fig. 2).

By means of a packet of programs from ACDLabs, we have calculated ^{13}C spectra for the both resonance structures, **16**(**N$^+$**) and **16**(**O$^+$**). As is seen from simulated spectra (Figs. 10 and 11), experimental values of chemical shifts for C-1a and C-4a are in between predicted ones, being closer to values calculated for resonance structure **16**(**O$^+$**), as a sequence of greater contribution of the latter in the mesomeric structure. Elongation of conjugated system in structure **16** is also evidenced by a yellow color of the substance.

It is interesting to note that 2D HMBC spectrum of compound **16** displays the same set of cross-peaks (for proton at C-2, carbon C-2 and carbon C-3a) as in the spectra of compounds **2** and **10** (H-2/C-3′, H-2/C-3, H-2/C-1a, H-2/C-1b, H-2/C-7′; H-2a/C-1a; C-3a/H-2a, C-3a/H-5a,6a,7a,8a) which confirms that the compounds contain the same heterocyclic core and the same set of adjacent atoms.

3.3. Liquid chromatography–accurate mass spectrometry

Q-TOF LC–MS instrument was operated as a useful adjunct to the other techniques, to assist in identifying compounds. The

Table 8
LC/QTOF-MS analytical data of compounds **1**–**16** (**16-HCl**).

Short name	Retention time (min)	Molecular formula	Experimental mass	Theoretical mass	Δm [ppm]
TMCP-H (**1**)	8.00	$C_{16}H_{19}NO$	241.1463	241.1467	1.4
TMCP-018 (**2**)	12.81	$C_{21}H_{29}NO$	311.2247	311.2249	0.82
TMCP-020 (**3**)	14.41	$C_{23}H_{33}NO$	339.2558	339.2562	1.16
TMCP-2201 (**4**)	11.21	$C_{21}H_{28}FNO$	329.2153	329.2155	0.49
TMCP-200 (**5**)	4.67	$C_{22}H_{30}N_2O_2$	354.2303	354.2307	1.16
TMCP-1220 (**6**)	4.73	$C_{23}H_{32}N_2O$	352.2515	352.2515	0.19
TMCP-1220-azepane (**7**)	4.85	$C_{23}H_{32}N_2O$	352.2516	352.2515	−0.37
A-836,339 (**8**)	5.22	$C_{16}H_{26}N_2O_2S$	310.1715	310.1715	0.11
TMCP-H (thermal isomer) (**9**)	7.30	$C_{16}H_{19}NO$	241.1464	241.1467	1.01
TMCP-018 (thermal isomer) (**10**)	12.13	$C_{21}H_{29}NO$	311.2249	311.2249	0.05
TMCP-020 (thermal isomer) (**11**)	13.79	$C_{23}H_{33}NO$	339.2564	339.2562	−0.56
TMCP-2201 (thermal isomer) (**12**)	10.53	$C_{21}H_{28}FNO$	329.2156	329.2155	−0.26
TMCP-200 (thermal isomer) (**13**)	4.11	$C_{22}H_{30}N_2O_2$	354.2311	354.2307	−0.91
TMCP-1220 (thermal isomer) (**14**)	4.22	$C_{23}H_{32}N_2O$	352.2516	352.2515	−0.33
TMCP-1220-azepane (thermal isomer) (**15**)	4.37	$C_{23}H_{32}N_2O$	352.2516	352.2515	−0.48
TMCP-018 acidic (**16**)	5.92	$C_{21}H_{29}NO$ (**16-HCl**)	311.2245 (**16-HCl**)	311.2249 (**16-HCl**)	1.29 (**16-HCl**)

resolution was higher than 20,000, which enabled us to determine exact masses of ions formed from a molecule. Based on these data, the chemical formulas of unknown substances were ascertained by means of MassHunter Qualitative Analysis B.05.00 software. Using this instrument, we have also measured retention times (in above-mentioned conditions of chromatographic separation). Similar to GC–MS, LC–MS of chloride (**16**), gave rather ion corresponding to **16-HCl** than parent ion for original structure **16**.

The data for compounds **1**–**16** and **16-HCl** are listed in Table 8.

4. Conclusion

In the investigations reported, a series of compounds from a new class of synthetic cannabimimetics bearing 2,2,3,3-tetramethylcyclopropanecarbonyl moiety were identified. Analytical characteristics obtained for the compounds from this new class of 'designer drugs' will make possible their reliable identification during forensic examination.

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